Acetaminophen Overdose: What Practitioners Need to Know

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Overview and Epidemiologic Considerations

Acetaminophen (APAP) is a highly effective analgesic and antipyretic agent that is safely used by millions of people every day. However, APAP is also a dose-dependent hepatotoxin that is present in over 600 marketed products and can cause acute pericentral liver injury when taken in doses exceeding 6 to 10 grams/day (Table 1). APAP overdose is the most common cause of drug-induced liver injury in the United States, with ≈ 60,000 cases reported each year, and also accounts for nearly 50% of adult acute liver failure (ALF) cases.[1] Intentional APAP overdose as a suicide gesture accounts for a majority of these cases, but there has been a significant increase in nonintentional APAP overdose cases over the past 2 decades.[2] Overall mortality remains low (< 1%) in intentional APAP overdose patients who receive NAC promptly. However, nearly 50% of the APAP ALF cases are attributed to "therapeutic misadventures"—patients who frequently ingest multiple APAP-containing products and present with more advanced encephalopathy and liver injury.[3] Because there are at least ≈500 deaths each year in the United States attributed to APAP overdose, there are increasing calls for regulatory actions regarding APAP dosing, dispensing, packaging, and coformulation with opioid analgesics.

Diagnosis and Clinical Presentation

Most patients with APAP overdose have minimal or nonspecific symptoms such as malaise, abdominal pain or nausea, and vomiting at presentation. A detailed medication history can help ascertain total APAP exposure but can be challenging in patients with polydrug overdose or advanced encephalopathy. The Rumack-Matthew nomogram to predict the likelihood of hepatotoxicity is recommended for initial assessment of all patients with a single time-point overdose (Fig. 1).[4] Although APAP is rapidly absorbed from the gastrointestinal tract, a repeat serum APAP level 4 hours after initial presentation is advisable to better define the risk of liver injury. Of note, the serum APAP level may be low or undetectable in patients who overdose over several days, and NAC should not be delayed whenever there is any clinical suspicion of APAP overdose. Serum acetaminophen-protein adducts are covalent adducts of APAP with a much longer half-life than the parent compound, which can be a helpful diagnostic tool in ambiguous cases, but this assay is not commercially available.[5]

Serum aminotransferase levels are frequently normal shortly after intentional APAP overdose but may rapidly increase during the first 24 hours of hospitalization. Some subjects may present with an isolated metabolic or lactic acidosis with or without acute kidney injury or an elevation in their international normalized ratio (INR) (Table 2). All patients with elevated serum aminotransferase levels should be evaluated for other etiologies of acute liver injury (ie hepatitis A, B, C; ischemia; pancreaticobiliary disease), as well as ingestion of other illicit substances (Table 2). A rapid assessment of the severity of liver injury is performed by a combination of clinical (grade of encephalopathy) and laboratory (liver chemistries, creatinine, INR, arterial PH, arterial lactate, and factor V assay) parameters. An early assessment of disease severity can help determine the

Abbreviations: AGA, The American Gastroenterological Association; AKI, acute liver injury; ALF, acute liver failure; ALFSG, Acute Liver Failure Study Group; ALT, alanine aminotransferase; APACHE II, Acute Physiology and Chronic Health Evaluation II; APAP, acetaminophen; AST, aspartate aminotransferase; CMV, cytomegalovirus; CVVH, continuous veno-venous hemofiltration; EBV, Epstein-Barr virus; ES, acetaminophen hydrocodone; FDA, US Food and Drug Administration; HBP, high blood pressure; HP, hydrocodone bitartrate and acetaminophen; ICU, intensive care unit; IgE, immunoglobulin-E; INR, international normalized ratio; IV, intravenous; MELD, Model for End-Stage Liver Disease; NAC, N-acetylcysteine; NSAID, nonsteroidal anti-inflammatory drugs; OTC, over-the-counter; SOFA, Sequential Organ Failure Assessment.

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TABLE 1 Acetaminophen Content of Some Commonly Used OTC Products

OTC Products	Acetaminophen Per Dose (mg)
Analgesics/antipyretics	
Children's Tylenol products	80-160 mg, 160 mg/5 ml*
Excedrin products	325-500 mg
Goody's Extra Strength powder products	250-500 mg
Goody's Headache Relief Shot	1000 mg/60 ml*
Midol products	500 mg
Midrin	325 mg
Pamprin products	250 mg
Tylenol Regular Strength	325 mg
Tylenol Extra Strength	500 mg
Tylenol Muscles Aches & Body pains/Arthritis Pain	650 mg
Cold, cough, and sinus products	
Alka-Seltzer products	325 mg
Coricidin HBP Maximum Strength Flu	500 mg
Delsym Cough and Night Time Cold & Cough	650 mg/20 ml*
Mucinex Fast-Max, all tablet/caplet products	325 mg
Mucinex Fast-Max, all-liquid products	650 mg/20 ml*
Robitussin Daytime Cold and Flu	325 mg
Sudafed PE Pressure and Pain and Cough	325 mg
Tylenol Sinus/Cold, all products	325 mg
Vicks Dayquil/Nyquil, all tablet/caplet products	325 mg
Vicks Dayquil Severe Cold & Flu Liquid	325 mg/15ml*
Vicks Nyquil Severe Cold & Flu Liquid	650 mg/30 ml*
Sleep aids	
Legatrin PM	500 mg
Tylenol PM	500 mg
Unisom PM Pain	325 mg

*Recommended single dose by manufacturer. The maximum total daily dose of acetaminophen containing products should not exceed 3000 mg (3 grams total). For further information regarding additional OTC products, see http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm165107.htm

Abbreviation: HBP, high blood pressure.

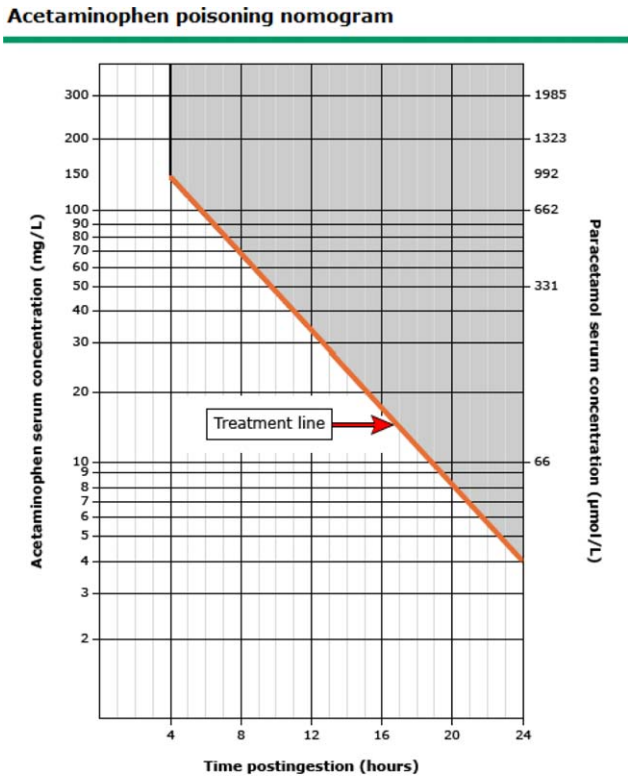

Figure 1 Modified Rumack-Matthew nomogram in APAP overdose. The modified Rumack-Matthew nomogram should only be used in patients with one time-point APAP ingestion. Subjects with a serum APAP level above the line are at risk for developing hepatotoxicity and should be hospitalized and given NAC for a minimum of 24 hours. The serum APAP level should be plotted in relationship to the estimated time of oral ingestion and should be repeated 4 hours after presentation in subjects with an unreliable history. The nomogram should not be used in ingestions that occurred > 24 hours prior to presentation or in patients who have overdosed over several days. This figure has been adapted from N Engl J Med.[4]

appropriate level of care for a given patient (ie general floor vs intensive care unit [ICU]). A psychiatric and social work evaluation of all patients with intentional APAP overdose should be initiated in parallel with their NAC treatment to maximize patient safety and avoidance of further harm.

Standard Treatment

All patients who present within 4 hours of APAP overdose should receive ipecac syrup to induce vomiting—or nasogastric lavage to remove pill fragments, followed by activated charcoal to reduce APAP absorption. NAC, which repletes the intrahepatic glutathione stores, also should be administered promptly via oral or intravenous (IV) route based on the patient's clinical condition.[4] Of note, NAC is a pungent sulfa drug that can cause significant nausea and vomiting in 20% to 30% of patients, and IV NAC can lead to rash and a non-IgE–mediated hypersensitivity reaction. Recently, a randomized trial has shown better tolerance and fewer side effects with a 12-hour IV regimen of NAC versus the standard 20-hour IV regimen, but confirmatory studies are needed[6] (Table 3). The incidence of hepatotoxicity is < 10% in those receiving NAC within 8 hours of ingestion but increases to 40% if NAC is delayed > 16 hours.

The goal of supportive care is to provide the optimal environment for hepatic recovery, vital organ support, and prevention and treatment of complications. General supportive measures include volume resuscitation and vasopressor support, monitoring for bleeding complications, monitoring and treatment of infections, respiratory support, avoidance of nephrotoxins, and renal support as needed.[7] Monitoring and treatment of hypoglycemia and hypophosphatemia are also important. Therefore, liver chemistries, renal function, INR, acid base status, and factor V should be checked every 12 hours. Subjects with no evidence of liver injury, coagulopathy, or kidney injury at 24 hours after presentation may have NAC discontinued and be treated supportively. In contrast, patients with evidence of early

TABLE 2 Clinical Features of APAP Overdose

Detailed history	Review all prescription and OTC medications. Total dose ingested > 4 grams Risk factors: fasting, alcohol use, concomitant medications, polypharmacy, opioid congeners Usually > 10 grams in 24 hours Single timepoint ingestion: Use Rumack-Matthew nomogram at presentation and 4 hours later Staggered/nonintentional overdose: Serum APAP levels may be low or undetectable. Give NAC whenever APAP overdose suspected.
Evaluation of other causes of acute hepatocellular liver injury	Hepatitis A, B, C; CMV; EBV Pancreaticobiliary disease, vascular thrombosis, pancreatitis, ischemia Others etiologies based on risk factors
Establish diagnosis	Serum APAP level Urine toxicology screen Blood alcohol level Hep A IgM, HBsAg, anti-HBc, HCV-RNA Liver ultrasound with Doppler
Severity assessment	Serum AST, ALT, total bilirubin (most have normal bilirubin at presentation) Peak ALT not seen till 48-72 hours INR Serum creatinine, bicarbonate, phosphate level 50% of ALF patients develop AKI Arterial pH and lactate Factor 5 level Encephalopathy assessment (Grade 0-4)
ICU care, if any of these features present	Encephalopathy grade 1 or higher Renal failure Metabolic acidosis Hypotension
Transfer to liver transplant center if	Encephalopathy grade 2 or higher Intubated, pressors, hemodialysis

Abbreviations: AKI, acute kidney injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CMV, cytomegalovirus; EBV, Epstein-Barr virus.

liver injury should receive a full 72 hours of NAC therapy, and those with poor prognostic indicators should be identified for early liver transplantation (LT) evaluation (Table 4).

Prognosis and Outcomes

Transplant-free survival from APAP-related ALF is significantly higher (70%) compared to ALF from idiosyncratic drug reactions (< 25%) or other causes of ALF (0%-50%).[8] Multiple prognostic scoring systems have been evaluated to identify the patients at increased risk of death without LT from APAP ALF (Table 3).[9] The King's College criteria with or without arterial lactate levels are the most commonly used criteria to list patients for LT. In a large multicenter prospective study of 275 APAP ALF patients, 178 (65%) patients survived without LT, 23 (8%) patients underwent LT, and 74 (27%) patients died.[3] The Apache II (Acute Physiology and Chronic Health Evaluation II) score yielded higher sensitivity but slightly lower specificity than King's College criteria. One-year survival after LT for APAP ALF is ≈73%.[10] For APAP hepatotoxicity patients not requiring LT, the mean length of stay for intentional overdose patients is 4 days, and for nonintentional overdose patients it is 9 days.

TABLE 3 Treatment and Management of APAP Overdose

Initial Measures on Presentation
Within 4 hours of ingestion
Ipecac syrup, 15 ml once; repeat in 20 minutes if needed
Nasogastric lavage of pill fragments
Activated charcoal, 1 g/kg body weight (maximum dose 50 grams)
Within 16 hours of Ingestion
NAC, oral or intravenous
Oral loading: 140 mg/kg followed by 70 mg/kg every 4 hours for 17 doses or until INR < 1.5
nausea and vomiting in 20%, mix with carbonated beverages to improve tolerance; prochlorperazine (Compazine) 10 mg, metoclopramide (Reglan) 10 mg, or ondansetron (Zofran) 4 mg by mouth or IV; consider IV NAC if refractory nausea and vomiting
Intravenous loading: 150 mg/kg in 250 ml dextrose 5% over 1 hour, then 50 mg/kg in 500 ml dextrose 5% over 4 hours; then 125 mg/kg in 1000 ml dextrose 5% over 19 hours; 100 mg/kg in 1000 ml dextrose 5% over 24 hours for 2 days or until INR is less than 1.5. Contraindicated in sulfa allergy.
IV NAC requires telemetry monitoring for arryhythmias and hypotension. Anaphylactoid reactions with urticaria or wheezing should have the infusion stopped and receive IM epinephrine, IV diphenhydramine, corticosteroids and albuterol. Resumption of infusion only in a monitored setting and consultation with local poison control center. If hypotension or angioedema, give fluids, steroids, and epinephrine and do not resume IV NAC (consider oral NAC with careful monitoring)
Minimum duration of NAC administration is 24 hours if no signs of liver injury or renal failure at 24 hours and 72 hours if evidence of liver injury.
IV NAC is generally preferred in pregnant women to maximize drug levels to fetus and also for individuals with short gut or ileus.
General Supportive Measures
Quiet and comfortable environment
Nutritional support
Monitoring of laboratory measures (every 12 hours)
Blood glucose monitoring every hour
Intravenous fluids if hypotension
Frequent screening for infection, low threshold for starting antimicrobial agents
Avoid correction of coagulopathy except for active bleeding or invasive procedures
Avoid nephrotoxic agents (NSAIDs, aminoglycosides)
Frequent monitoring of neurological status
Intensive Care
Urgent liver transplant evaluation
Encephalopathy grade I or II
Computed tomography of head to evaluate bleeding/cerebral edema
Avoid sedation; propofol and midazolam preferred for severe agitation
Keep head of bed > 30 degrees to avoid intracranial hypertension
Encephalopathy grade III or IV
Avoid fever; goal temperature ~ 36°C
Intubation and mechanical ventilation
Vasopressor support if persistent hypotension despite IV fluids
Renal support: CVVH preferred over hemodialysis
Invasive monitoring of intracranial pressure, treat with hyperventilation, mannitol or hypertonic saline; barbiturate coma for refractory cases

Abbreviations: CVVH, continuous veno-venous hemofiltration; NSAID, nonsteroidal anti-inflammatory drugs.

Prevention of Acetaminophen Overdose

Several steps have been taken by regulatory authorities to change the labeling and dispensing of the hundreds of prescription and over-the-counter (OTC) products containing APAP (Table 5). In 1998, the United Kingdom limited the sale of OTC APAP to 8 grams and required blister packaging of APAP products. This resulted in significant decrease in the APAP overdose cases, number of admissions to liver units, and number of liver transplants due to APAP overdose.[11] In 2006, the FDA enacted changes in the labeling of

TABLE 4 Prognostic Scoring Systems Used to Identify Patients at High Risk of Mortality Without Liver Transplantation Due to APAP-Related ALF

Scoring System	Key Components	Sensitivity	Specificity
King's College criteria	Arterial pH < 7.30 or	55%	93%
	Prothrombin time > 100 plus Encephalopathy grade > 2 plus Serum creatinine > 3.4 mg/dl	58%	95%
Arterial lactate	3.5 mmol/l on presentation or	81%	72%
	> 3 mmol/l after fluid resuscitation	81%	77%
Modified King's College criteria	King College criteria plus arterial lactate > 3 mmol/l following resuscitation	91%	71%
APACHE II	Score > 15 at 24-hour postadmission	79%	97%
SOFA score	Score > 8 at admission	67%	66%
MELD score	MELD > 30	97%	68%
ALFSG index	Coma grade, bilirubin, INR, serum phosphate, M-30 (serum marker of apoptosis)	86%	65%
Routinely used indicators of poor prognosis	Arterial pH < 7.3 Arterial lactate > 3 mmol/l following resuscitation Encephalopathy grade III or IV Factor V ratio < 20%	Presence of 2 or more factors associated with poor transplant-free survival	

Sensitivities and specificities stated for transplant-free survival.
Abbreviations: ALFSG, Acute Liver Failure Study Group; MELD, Model for End-Stage Liver Disease; SOFA, Sequential Organ Failure Assessment.

all OTC products that contain APAP to include extra warnings. More recently, the FDA has limited the dose of APAP in prescription combination products to a maximum of 325 mg per tablet and also included black-box warnings on these products regarding their APAP content. In addition to regulatory actions, patient education by health care providers is

TABLE 5 Regulatory and Educational Measures Undertaken to Reduce the Incidence of APAP Overdose

United Kingdom legislation, 1998	Acetaminophen sale in blister pack only Maximum tablets in OTC packets restricted to 16 (500-mg strength) Maximum tablets issued by pharmacist restricted to 32 (500-mg strength)			
FDA, 2006	Labeling changes on all APAP containing OTC products Black-box "liver warning" Increase font size and highlighting of the ingredient name "acetaminophen." Warning for patients with liver disease and those that consume 2-3 alcoholic beverages/day to consult a doctor before using the product			
FDA, 2014	Prescription APAP combination products limited to no more than 325 mg acetaminophen per dosage unit Combination product labels to include black-box warning regarding APAP content and potential for hepatotoxicity OTC products still allowed to contain > 325 mg/dose, and many have 500-650 mg/dose (see Table 1)			
	Discontinued		New Formulations	
	Brand	Generic	Brand	Generic
	Lortab Elixir	Hydrocodone-acetaminophen 2.5-500 mg/5 ml oral solution 7.5-500 mg/5 ml oral solution	NAHycet	Hydrocodone-acetaminophen 2.5-108 mg/5 ml oral solution 7.5-325 mg/15 ml oral solution
	Lortab	Hydrocodone-acetaminophen 7.5-500 mg tablet	NorcoVicodin-ES	Hydrocodone-acetaminophen 7.5-325 mg tablet7.5-300 mg tablet
	Lortab	Hydrocodone-acetaminophen 10-500 mg tablet	NorcoVicodin-HP	Hydrocodone-acetaminophen 10-325 mg tablet10-300 mg tablet
	Percocet	Oxycodone-acetaminophen 7.5-500 mg tablet	Percocet	Oxycodone-acetaminophen 7.5-325 mg tablet
	Percocet	Oxycodone-acetaminophen 10-650 mg tablet	Percocet	Oxycodone-acetaminophen 10-325 mg tablet
	Phrenilin Forte	Butalbital-acetaminophen 50-650 mg capsule	Phrenilin	Butalbital-acetaminophen 50-325 mg capsule
AGA Medicine Safety Campaign, 2013	Emphasis on patient education regarding the safety of OTC pain medications. A short online video at http://gutcheck.gastro.org An infographic available online and for use in doctor's offices. Other educational materials for patients.			

Abbreviations: ES, acetaminophen hydrocodone; HP, hydrocodone bitartrate and acetaminophen.

extremely important. The American Gastroenterological Association (AGA) has launched an innovative campaign comprising of a short online video (http: //gutcheck.gastro.org) and other education materials to help raise awareness among patients regarding OTC and prescription medications containing APAP. However, a recent prospective study has demonstrated the limitations of written and even verbal instructions to patients regarding the potential for inadvertent APAP toxicity when using multiple products.[12]

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References

1. Nourjah P, Ahmad SR, Karwoski C, Willy M. Estimates of acetaminophen (Paracetomal)-associated overdoses in the United States. Pharmacoepidemiol Drug Saf 2006;15(6):398-405.
2. Myers RP1, Li B, Fong A, Shaheen AA, Quan H. Hospitalizations for acetaminophen overdose: a Canadian population-based study from 1995 to 2004. BMC Public Health 2007;7:143.
3. Larson AM, Polson J, Fontana RJ, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology 2005;42(6):1364-1372.
4. Smilkstein MJ, Knapp GL, Kulig KW, Rumack BH. Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose. N Engl J Med 1988;319:1557-1562.
5. Davern TJ, James LP, Hinson JA, et al. Measurement of serum acetaminophen–protein adducts in patients with acute liver failure. Gastroenterology 2006;130:687-694.
6. Bateman DN, Dear JW, Thanacoody HK, et al. Reduction of adverse effects from intravenous acetylcysteine treatment for paracetamol poisoning: a randomised controlled trial. Lancet 2014;383(9918): 697-704.
7. Stravitz RT, Kramer AH, Davern T, et al. Intensive care of patients with acute liver failure: recommendations of the U.S. acute liver failure study group. Crit Care Med 2007;35:2498-508.
8. Ostapowicz G, Fontana RJ, Schiødt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med 2002;137(12):947-954.
9. Craig DG, Ford AC, Hayes PC, Simpson KJ. Systematic review: prognostic tests of paracetamol-induced acute liver failure. Aliment Pharmacol Ther 2010;31(10):1064-1076.
10. Bernal W, Wendon J, Rela M, et al. Use and outcome of liver transplantation in acetaminophen-induced acute liver failure. Hepatology 1998;27:1050-1055.
11. Hawton K1, Simkin S, Deeks J, et al. UK legislation on analgesic packs: before and after study of long term effect on poisonings. BMJ 2004;329(7474):1076.
12. Serper M, et al. Effect of enhanced risk communication on patient comprehension of concomitant use warnings for APAP- containing products: A randomized Trial (Abstract). Hepatology 2013;58;1722.